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REVIEW

Scoping Review on Use of Drugs Targeting Interleukin 1 Pathway in DIRA and DITRA

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ABSTRACT

Introduction: Deficiencies in interleukin (IL)-1 receptor (IL-R) antagonist (DIRA) and IL-36R antagonist (DITRA) are rare genetic autoinflammatory diseases related to alterations in

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antagonists of the IL-1 pathway. IL-1 antagonists may represent therapeutic alternatives. Here, we aim to provide a scoping review of knowledge on use of IL-1-targeting drugs in DIRA and DITRA.
Methods: An a priori protocol was published, and the study was conducted using the methodology described in the Joanna Briggs Institute Reviewer's Manual and the recently published PRISMA Extension for Scoping Review statement. A three-step search using MEDLINE and EMBASE databases until March 2018 with additional hand searching was performed. Data charting was performed. The search, article selection, and data extraction were carried out by two researchers independently.
Results: Twenty-four studies on use of anti-IL-1 drugs were included [15 studies including patients with diagnosis of DIRA ($n = 19$) and 9 studies including patients with diagnosis of DITRA ($n = 9$)]. Most studies followed a multicenter observational design. Among all patients who received treatment with anti-IL-1 drugs, nine and four mutations in *IL1RN* and *IL36RN* were found, respectively. Patients with DIRA were treated with anakinra ($n = 17$), canakinumab ($n = 2$), or rinolacept ($n = 6$). All patients with DITRA were treated with anakinra, and only one case was also treated with canakinumab. Time-to-response frequencies were evaluated as immediate, short, and medium–long term for DIRA (17/17, 15/17, and 9/10,

respectively) and DITRA (7/9, 3/9, and 2/9, respectively). Most DITRA patients in whom anti-IL-1 treatment failed experienced good response to anti-tumor necrosis factor alpha or anti-IL-12/23 drugs. The safety profiles of treatments were similar in both diseases.

Conclusions: Evidence on use of anti-IL-1 drugs in DIRA and DITRA is scarce and based on observational studies. Larger studies with better methodological quality are needed to increase confidence in use of these drugs in patients with DIRA and DITRA.

INTRODUCTION

Hereditary autoinflammatory diseases are a heterogeneous group of rare genetic disorders in which an exaggerated innate immune response is the pathogenic basis of recurrent episodes of inflammation. These inflammatory episodes affect the skin, joints, bones, eyes, gastrointestinal tract, and central nervous system in association with nonspecific signs of systemic inflammation and a lack of high-titer circulating auto-antibodies or antigen-specific T cells [1].

Alterations in the interleukin (IL)-1 pathway have been shown to be involved in the pathogenesis of some diseases. IL-1 contributes to coordination of the early response of the immune system to exogenous and endogenous antigens, serving as a prototypic alarm cytokine [2]. The interleukin IL-1 family comprises 11 members, including seven proinflammatory agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ) and four defined or putative antagonists [IL-1 receptor (IL-1R) antagonist (IL-1RA), IL-36R antagonist (IL-36RA), IL-37, and IL-38], which exert antiinflammatory activity [3]. IL-1-related hereditary diseases are considered secondary to genetic defects in both activating and inhibitory pathway molecules. Notably, cryopyrin-associated autoinflammatory syndromes (CAPSs) are primary diseases caused by alterations in IL-1 pathway agonists. Moreover, several new diseases associated with alterations in IL-1RA, such as deficiency of IL-1RA (DIRA) and deficiency of IL-36RA (DITRA), have recently been identified. IL-1RA, encoded by the *IL1RN* gene, functions as a decoy protein that binds to IL-1R but does not result in any response signal. IL-36RA, encoded by the *IL36RN* gene, has been shown to specifically inhibit IL-1-induced activation of nuclear factor-κB. Both IL-1RA and IL-36RA are encoded on chromosome 2 and show 44% homology. However, IL-1RA is expressed ubiquitously, whereas IL-36R expression is restricted to epithelial cells, including those in the skin [4]. This fact may explain the observation that both DIRA and DITRA share similar skin manifestations but with the difference that extracutaneous involvement is observed in DIRA.

DIRA is a rare life-threatening autoinflammatory disease first described in 2009 [1, 5]. DIRA is caused by autosomal recessive mutations in the *IL1RN* gene and presents clinically as early onset of generalized cutaneous pustulosis, multifocal osteomyelitis, and high levels of acute-phase reactants. DITRA is a more recently described hereditary autoinflammatory disease caused by homozygous or compound heterozygous mutations in the *IL36RN* gene and characterized by repeated flares of generalized pustular psoriasis associated with high fever, asthenia, and systemic inflammation [6].

Various treatment strategies, such as antiinflammatories [nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids], antimicrobial agents (antifungal and antibacterial agents), and immunosuppressants (methotrexate, cyclosporine, inhibitors of tumor necrosis factor-α, and anti-IL-17 monoclonal antibodies), have been applied for treatment of DIRA and DITRA, with variable responses. As knowledge of the pathogenesis of these diseases has improved, increasingly specific treatments have been developed. Accordingly, four drugs targeting the IL-1 pathway have been developed. These include anakinra, a recombinant IL-1RA that competes with IL-1R agonists for its receptor [7]; rilonacept, which acts as a soluble decoy to prevent activation of IL-1RI [8];

canakinumab, a human monoclonal antibody targeting IL-1β [9]; and MABp1, an anti-IL-1α monoclonal antibody [10]. Although the specificities of their mechanisms of action suggest the feasibility of achieving sufficient efficacy, the molecular differences found in both DIRA and DITRA can yield different levels of response. Moreover, these drugs are associated with short- and long-term adverse effects. Therefore, it is necessary to consider treatments with the best risk–benefit balance.

However, because DIRA and DITRA are rare diseases that have only been identified within the last decade, available evidence on use of IL-1 pathway-modulating agents for their treatment is scarce, and no secondary research has been published to date. Therefore, it is necessary to synthesize evidence derived from primary studies on use of anti-IL-1 drugs for treatment of DIRA and DITRA, map the published articles, and study the epidemiology of genetic characteristics and anti-IL-1 drug efficacy/safety results based on available evidence. Such analysis will help identify gaps in knowledge and formulate questions that can be answered through systematic review.

A scoping review is a form of scientific synthesis that addresses an exploratory research question, aimed at mapping key concepts and identifying research gaps related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge [11]. Scoping reviews contribute to integrating optimal research evidence available with clinical experience and patient values to improve care, health, and cost outcomes [12].

Accordingly, in this work, we present the results of a scoping review on use of anti-IL-1 drugs in dermatological diseases whose protocols have been previously published [13]. In this first summary, we report and discuss evidence regarding use of these drugs in patients with DIRA/DITRA.

METHODS

A scoping review protocol was a priori published [13]. The study was conducted and reported using the methodology described in the Joanna Briggs Institute Reviewer's Manual [14] and the PRISMA Extension for Scoping Reviews [15]. When necessary, authors of articles were contacted to obtain more data or clarify issues.

Eligibility Criteria

To be included in the review, papers had to show evidence of use of anti-IL-1 drugs (anakinra, canakinumab, rilonacept, or AMB1) in patients with DIRA or DITRA. Studies were included if they were written in English, involved human participants, and described the conditions formulated in the research question, regardless of publication date or format. Articles were excluded if they did not fit into the conceptual framework of the study (i.e., if a case of DIRA or DITRA was described as not having been treated with anti-IL-1 drugs). Nonscientific reviews and opinion articles were excluded.

Literature Search

We performed a three-step literature search to identify and locate all relevant studies on use of anti-IL-1 drugs in dermatological diseases, and subsequently selected articles related to use of these drugs in patients with DIRA or DITRA. The first step was performed on 9 March 2018 and entailed a limited search strategy [SEARCH QUERY ('skin disease' AND (('interleukin 1-beta'/exp OR 'interleukin 1beta') OR 'interleukin 1')) AND 'therapy'] in MEDLINE and EMBASE databases. Next, we extracted keywords from titles, abstracts, and indexing categorizations and used them to perform a new search on 10 March 2018 with a more complex strategy (Table S1 in Supplementary Information). Results were ordered by disease based on review of the title and abstract. Subsequently, sources related to DIRA and DITRA were selected. The third step involved a new search using the reference lists of all selected reports and articles for identification of additional relevant studies. The literature search and title and abstract filtering were carried out independently by two researchers (F.G.-G. and J.L.S.-C.).

Data Charting

A data charting form was jointly developed by two reviewers to determine which variables to extract. A pilot test was carried out with three studies, and the chosen variables were included in a .csv file. The two reviewers independently charted the data, discussed the results, and continuously updated the data charting form in an iterative process. Finally, variables related to patients (disease, drug, treatment response, and safety profile) and to the study design and metadata from primary sources were reported (Tables 1, 2, 3, and 4; Tables S1–S4 in Supplementary Files).

Collating, Summarizing, and Reporting Results

We grouped the articles by disease type. The results of the comprehensive search were presented using a PRISMA flow diagram. A narrative and qualitative synthesis of DIRA and DITRA mapping studies and epidemiological, genetics, and efficacy and safety findings were elaborated using tables and figures.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Protocol versus Overview

Our planned search strategy published in *Dermatology and Therapy* was compared with the final reported review methods. Due to time and funding limitations, we decided to select only studies published in English.

RESULTS

Search Results

From 3708 articles regarding use of anti-IL-1-related drugs in dermatological diseases, after filtering duplicates and selecting studies according to title, abstract, and keywords, 77 studies met the criteria for full-text review. Of these, 21 [DIRA ($n = 13$) and DITRA ($n = 8$)] fulfilled the inclusion criteria. After reviewing citations of references for these studies, three new articles [DIRA ($n = 2$) and DITRA ($n = 1$)] were obtained. Finally, 24 studies, including 15 describing DIRA ($n = 15$) and 9 describing DITRA ($n = 9$), were included in the scoping review. A reference list of all included and excluded articles with reasons for exclusion is presented in Fig. S1 in Supplementary Information.

Evidence for Mapping the Studies of IL-1-Based Treatment in Patients with DIRA/DITRA

DIRA

Fifteen studies, published between 2009 and 2017 as full papers ($n = 11$) or congress abstracts ($n = 4$), followed mainly an observational design (13 case reports, 1 case series), and only one was an intervention study. Only three studies (20%) had an a priori protocol that was included in a public registry. Twelve (63.1%) were elaborated as multicentric studies involving up to nine different institutions. The average numbers of authors and affiliations per article were 11 (range 3–45) and 5 (range 2–14), respectively, and different medical specialties were involved [pediatrics ($n = 11$), genetics ($n = 11$), rheumatology ($n = 7$), allergy–immunology ($n = 6$), and dermatology ($n = 5$)], although authors from academia ($n = 4$) and the pharmaceutical industry ($n = 1$) were also included. Most studies were performed in the USA [8], with the National Institutes of Health (NIH, Bethesda, MD, USA) and associated centers of institutions participating in more studies ($n = 10$; Table S1 in Supplementary Information). Other countries that also participated were Brazil ($n = 3$), Turkey ($n = 2$), Germany ($n = 1$), and Puerto Rico ($n = 1$). The studies were published in journals from disciplines such as rheumatology ($n = 5$), general medicine ($n = 4$), dermatology ($n = 3$), immunology ($n = 2$), and radiology ($n = 1$).

In seven (46.7%) and ten (66.7%) studies, disclosures related to the source of funding

Table 1 Characteristics of individual patients from DIRA studies included in the review

DIRA patient	Country	Age			Gender	Clinical features											Mutations	Ref.
		Gestation (weeks)	Onset (days)	Diagnosis (months)		Pustular dermatitis	Stomatitis	Localized swelling	Fever	Rash	Other skin conditions	Multiple bone lesions	Lung involvement	Liver/ spleen	Thrombosis	Other clinical		
#1	Canada	35.5	15	13	M	+	+	+	−	MS	P	+	−	−	−	1	Homozygous for IL1RN c.156_157delCA deletion	[1]
#2	The Netherlands	38	0	86	F	+	−	−	−	M	?	+	+	+	−	−	Homozygous for IL1RN c.229G > T (p.Glu77Ter) mutation	[1]
#3	The Netherlands	38	17	2	F	+	+	−	−	S	?	+	+	+	−	−	Homozygous for IL1RN c.229G > T (p.Glu77Ter) mutation	[1]
#4	Lebanon	38	5	20	M	+	+	−	−	S	P	+	−	−	−	2	Homozygous for IL1RN c.160C > T (p.Gln54Ter) mutation	[1]
#5	Lebanon	38	2	4	M	−	+	−	−	M	?	+	+	?	−	2	Homozygous for IL1RN c.160C > T (p.Gln54Ter) mutation	[1]
#6	Puerto Rico	34	8	114	M	−	−	+	−	M	PG	+	−	?	−	−	Homozygous for 175-kb deletion on chromosome 2q13[a]	[1]
#7	NA	33	10	1.5	M	+	−	−	−	MS	?	+	+	?	+	−	Homozygous for 175-kb deletion on chromosome 2q13[a]	[5]
#8	Brazil	NA	0	30	F	+	−	−	+	S	P/A	+	−	?	+	−	Homozygous for IL1RN c.213_227del AGATGTGGT ACCCAT (p.Asp72_Ile76del)	[35]
#9	Brazil	NA	0	27	F	−	−	−	+	MS	?	+	−	?	+	−	Compound heterozygous for IL1RN c.229G > T (p.Glu77Ter) and IL1RN c.140delC (p.T47TfsX4)	[35]

Table 1 continued

DIRA patient	Country	Age			Gender	Clinical features											Mutations	Ref.
		Gestation (weeks)	Onset (days)	Diagnosis (months)		Pustular dermatitis	Stomatitis	Localized swelling	Fever	Rash	Other skin conditions	Multiple bone lesions	Lung involvement	Liver/ spleen	Thrombosis	Other clinical		
#10	NA	NA	14	2	M	−	−	+	+	M	?	+	−	?	+	−	Compound heterozygous for IL1RN c.229G > T (p.Glu77Ter) mutation and 175-kb deletion on chromosome 2q13[a]	[36]
#11	Puerto Rico	31	165	180	M	+	−	−	+	S	?	+	−	?	+	−	Homozygous for 175-kb deletion on chromosome 2q13[a]	[19]
#12	NA	NA	30	1.5	M	−	−	+	+	M	?	+	−	?	−	?	NA	[34]
#13	Puerto Rico	37	60	5	M	+	−	−	+	S	?	+	+	?	−	3	Homozygous for 175-kb deletion on chromosome 2q13[a]	[29]
#14	Germany	38	NA	24	F	−	−	+	+	M	?	+	−	?	−	4	Homozygous for IL1RN c.840-6 bp deletion	[18]
#15	Puerto Rico	NA	7	3	F	+	−	−	?	M	P	+	+	?	−	?	Homozygous for 175-kb deletion on chromosome 2q13[a]	[30]
#16	Turkey	NA	365	144	F	+	−	−	−	M	?	+	+	+	−	?	Homozygous for IL1RN c.78G > A (p.Thr26X) mutation	[33]
#17	Turkey	NA	0	84	M	+	−	−	?	S	?	?	?	?	−	?	Homozygous for IL1RN (c.396delC) deletion[b]	[32]
#18	India	NA	21	5	F	−	−	+	?	M	?	+	?	?	−	?	Homozygous for 22.5-kb deletion spanning first four exons (two coding) of IL1RN[c]	[24]
#19	Brazil	NA	120	84	M	+	−	−	?	S	?	+	?	?	−	?	Compound heterozygous for IL1RN p.Ile74_Pro78del and p.Gln48Thr	[31]

M male, F female, P pathergy, PG pyoderma gangrenosum, M mild, MS mild–severe, A abscesses

1: central nervous system vasculitis; 2: conjunctival injection; 3: nonspecific inflammation of the whole intestine but without granulomas; 4: systemic inflammatory response syndrome (SIRS)

[a] A deletion of approximately 175 kb on chromosome 2q that includes six genes from a cluster of interleukin-1-related genes: IL1RN and the genes encoding interleukin-1 family, members 9 (IL1F9), 6 (IL1F6), 8 (IL1F8), 5 (IL1F5), and 10 (IL1F10)

[b] This frameshift mutation, which makes the stop codon at position c.534 disappear, results in a nonfunctioning protein

[c] Unreported intronic variant upstream to the exon 9 splice-acceptor site of unknown clinical significance in the IL1RI gene, which could potentially interfere with transcript splicing

Table 2 Characteristics of individual patients from DIRA studies included in the review (cont.)

DIRA patient	Anti-IL-1 drug	Initial dosage	Maintenance dosage	Duration (days)	Adjuvant corticosteroids	Reduction/withdrawal of corticosteroids	Initial efficacy	Short-term efficacy[a]	Medium/long-term efficacy[b]	Clinical efficacy	Analytical efficacy	Recurrence	Adverse events
#1	Anakinra	1 mg/kg/24 h	(1)	350	Yes	Withdrawal	Yes	Yes	Yes	Yes	Yes	Yes	Aggregate data
#2	Anakinra	1 mg/kg/24 h	(1)	1500	Yes	Withdrawal	Yes	Yes	Yes	Yes	Yes	Yes	Aggregate data
#3	Anakinra	1 mg/kg/24 h	(1)	40	Yes	Withdrawal	Yes	Yes	NA	Yes	Yes	Yes	Aggregate data
#4	Anakinra	1 mg/kg/24 h	(1)	14	Yes	Withdrawal	Yes	Yes	NA	Yes	Yes	Yes	Aggregate data
#5	Anakinra	1 mg/kg/24 h	(1)	30	Yes	Withdrawal	Yes	Yes	NA	Yes	Yes	Yes	Aggregate data
#6	Anakinra	1 mg/kg/24 h	(1)	100	Yes	Reduction	No	Yes	NA	Yes	No	Yes	Aggregate data
#7	Anakinra	5 mg/kg/24 h	2.5 mg/kg/24 h	180	No	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA
#8	Anakinra	1 mg/kg/24 h	2.5 mg/kg/24 h	Months	Yes	Withdrawal	Yes	Yes	NA	Yes	Yes	Yes	NA
#9	Anakinra	1 mg/kg/24 h	3 mg/kg/24 h	Months	Yes	Withdrawal	Yes	Yes	Yes	Yes	Yes	Yes	NA
#10	Anakinra	NA	NA	180	Yes	Withdrawal	Yes	Yes	Yes	Yes	Yes	NA	NA
#11	Anakinra	1 mg/kg/24 h	1 mg/kg/24 h	240	NA	NA	Yes	Yes	Yes	Yes	Yes	NA	None
#12	Anakinra	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	Yes	NA	None
#13	Anakinra	3 mg/kg/24 h	3 mg/kg/24 h	60	Yes	Withdrawal	Yes	Yes	NA	Yes	Yes	NA	NA
#14	Anakinra	NA	NA	270	NA	NA	Yes	Yes	No	Yes	Yes	NA	NA
#15	Anakinra	NA	6 weeks	NA	NA	NA	Yes	Yes	NA	Yes	Yes	NA	NA
#16	Canakinumab	150 mg ew 6 weeks	150 mg ew × 6 weeks	365	NA	NA	Yes	Yes	Yes	Yes	Yes	NA	None
#17	Anakinra	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
#18	Anakinra	1.5 mg/kg/24 h	(2)	365	Yes	Reduction	Yes	Yes	Yes	Yes	Yes	NA	NA
#19	Canakinumab	2 mg/kg ew 4 weeks	4 mg/kg ew × 4–6 weeks	NA	NA	NA	no	Yes	NA	Yes	Yes	NA	Generalized urticarial rash / Vomiting and diarrhea

ew every week

(1) The dosage was increased by 0.5 mg/kg/day at follow-up visits to achieve C-reactive protein less than 0.5 mg/dl and erythrocyte sedimentation rate less than 15 mm/h

(2) Reduced dosage because of generalized urticarial rash

[a] < 12 weeks

[b] > 24 weeks

Table 3 Characteristics of individual patients from DITRA studies included in the review

DITRA patient	Country	Age (Gestation weeks)	Onset (days)	Diagnosis (months)	Gender	Cutaneous presentation	Cutaneous clinical evolution	Fever	Elevated acute-phase reactants	Previous treatment	Mutations	Ref.
#1	Morocco	41	60	17	M	Multiple pustules appeared in the perioral and diaper area	Recurrent episodes of erythroderma	+	+	Cyclosporine	Homozygous for IL36RN c.80T > C (p.Leu27Pro) mutation	[1]
#2	NA	NA	1080	38	F	Generalized pustular lesions	Generalized	+	NA	Antibiotics Corticosteroids Acitretin Cyclosporine	Compound heterozygous for IL36RN c.227C > T (p.Pro76Leu) and c.338C > T (p.Ser113Leu) mutations	[1]
#3	NA	NA	Infancy	Adolescent	F	Generalized pustular psoriasis	Generalized pustular psoriasis	NA	+	Corticosteroids Acitretin Methotrexate Cyclosporine Adalimumab Infliximab	Homozygous for IL36RN c.115 + 6T > C mutation	[1]
#4	Tunisia	NA	14 years	3	M	Erythematous and scaly eruption over the scalp and perineum	Generalized exfoliative dermatitis	No	+	Corticosteroids Acitretin	Homozygous for IL36RN c.80T > C (p.Leu27Pro) mutation	[1]
#5	NA	NA	47 years	54 years	M	NA	NA	NA	NA	Acitretin Methotrexate Cyclosporine Infliximab	Heterozygous for IL36RN c.338C > T (p.Ser113Leu) mutation	[1]
#6	NA	NA	NA	NA	M	Generalized pustular lesions	Generalized erythema	NA	NA	Corticoids Acitretin Cyclosporine	Heterozygous mutation for IL36RN c338C > T (pSer113Leu)	[1]
#7	NA	NA	40 years	40 years	M	Scaly erythema on elbows	Severe flare of GPP	+	+	Antibiotics Corticosteroids Methotrexate Cyclosporine Adalimumab	Compound heterozygous for IL36RN c.142C > T (p.Arg48Trp) and IL36RN c.338C > T (p.Ser113Leu) mutations	[5]
#8	Morocco	37	60	8	F	Initially located at the diaper area	Generalized	+	+	Antibiotics Corticosteroids Acitretin	Compound heterozygous for L36RN c.T80C (p.Leu27Pro), c338C > T (p.Ser113Leu) and c.142C > T (p.Arg48Trp) mutations, and NSD1 (5q35.2-q35.3) microduplication	[35]

Table 3 continued

DITRA patient	Country	Age		Gender	Cutaneous presentation	Cutaneous clinical evolution	Fever	Elevated acute-phase reactants	Previous treatment	Mutations	Ref.
		Gestation (weeks)	Onset (days)	Diagnosis (months)							
#9	Denmark	38	90	4	F	Generalized pustular psoriasis	Generalized pustular psoriasis	NA	Normal	Antibiotics Corticosteroids Methotrexate	Compound heterozygous for *IL36RN* c.338C > T (p.Ser113Leu) and *NLRP3* c.2107C > A (p.Gln703Lys)	[35]

(five, public sources; one, public and pharmaceutical sources; and one without funding) or authors' conflicts of interest (CoIs) were declared, respectively. AMGEN (five authors), Novartis (two authors), and Lilly (two authors) were the pharmaceutical companies most frequently cited in CoIs by the authors.

DITRA

Nine studies related to use of anti-IL-1 drugs in DITRA were found. All were observational case report studies. No a priori design or registration was reported for any of these studies. Five of nine (55.5%) were multicenter studies (range 1–5). No centers participated in more than one study. Two were performed in Spain and France, and one each was performed in The Netherlands, USA, Italy, Denmark, and Germany. Articles were published between 2011 and 2018. Six papers were published in dermatology journals, two in rheumatology journals, and one in a pediatrics journal. Three were full papers, three were letters, and three were abstracts from conferences. The average numbers of authors and affiliations per article were 7.2 (range 4–15) and 3.22 (range 1–7), respectively. The most frequent specialties were dermatology in eight papers and genetics and pediatrics in five papers. One study [16] declared funds from Strasbourg High Throughput Next Generation Sequencing facility (GENOMAX) and INSERM UMR_S 1109. Four did not report funding or did not provide funding information. In two of the studies, the authors declared CoIs (Novartis and Sobi for three and two authors, respectively; these companies were the most frequently declared in CoIs). Three and four papers declared no CoIs or did not provide such information, respectively.

Evidence for Analysis of Epidemiology of IL-1-Based Agents in Treatment of Patients with DIRA/DITRA

DIRA

Individual data were obtained from 19 patients who had been treated with anakinra ($n = 17$) and canakinumab ($n = 2$). Eight of 19 (42.10%) patients were female. Of these 19 patients, 3

Table 4 Characteristics of individual patients from DITRA studies included in the review (cont.)

DITRA patient	Anti-IL-1 drug	Initial dosage	Maintenance dosage	Duration (days)	Adjuvant corticosteroids	Reduction/ withdrawal	Initial efficacy	Short-term efficacy[a]	Long-term efficacy[b]	Final treatment	Adverse events
#1	Anakinra	5 mg/kg/24 h	No	6	No	NA	Yes	No	NA	Acitretin/ etanercept	NA
#2	Anakinra	5 mg/kg/24 h	3 mg/kg/24 h	60	Yes	No	Yes	No	NA	Ustekinumab	Systemic infection
#3	Anakinra	No	3		No	NA	No	No	NA	Secukinumab	Renal and hepatic laboratory abnormalities; Rising white blood cell count; Deteriorating clinical status with progressive pustulation
#4	Anakinra	2–4 mg/kg/24 h	No	60	No	NA	Yes	Yes	NA	Anakinra	Pain at the injection site without erythema
#5	Anakinra	100 mg/24 h	NA	365	No	NA	Yes	Yes	Yes	Anakinra	NA
#6	Anakinra	NA	NA	NA	No	NA	Yes	No	No	Adalimumab/ methotrexate	NA
#7	Anakinra	100 mg/24 h	NA	224	No	NA	Yes	Yes	Yes	Anakinra	NA
#8	Anakinra//canakinumab	5 mg/kg/24 h//3 mg/kg every 8 weeks	NA/NA	90/NA	No//no	NA/NA	No//no	No//no	No//no	–	NA
#9	Anakinra	4 mg/kg/24 h	8 mg/kg/24 h	8 weeks	No	NA	Yes	No	No	Infliximab	NA

[a] < 12 weeks
[b] > 24 weeks

each were from Brazil and Puerto Rico, 2 each were from Turkey, Lebanon, and The Netherlands; and 1 each was from India, Canada, and Germany. Data from three patients could not be obtained. Seven of 11 (63.63%) patients were full-term infants, and 4 of 11 (36.36%) were preterm newborns. Data for eight patients were missing. Pustular dermatitis and localized swelling were observed in 12 and 6 patients, representing the most frequent symptom of onset of the disease. During disease evolution, patients presented with pustular skin rash (severe in 6 of 19 cases), multiple bone involvement (ribs being the most frequent site, in 17 of 19), fever (in 8 of 16), lung involvement (in 7 of 19), venous thrombosis (in 5 of 19), and elevation of acute-phase reactants (in 19 of 19). With respect to age at disease presentation, data were obtained from 18 patients. The median age was 14 days (range 0–365 days). Median age at diagnosis was 24 months (range 1.5–180 months). The median delay in diagnosis was 19.5 months (range 0.5–179.5 months). Seventeen of 18 (94.4%) patients had received previous treatment. Of these, 13 were treated with corticosteroids, 12 with antibiotics, 4 with NSAIDs, 3 with antifungals, 3 with acitretin, and 1 each with methotrexate, cyclosporine, intravenous immunoglobulins, azathioprine, thalidomide, and etanercept.

One study [17] presented aggregate data from six patients who had been treated with rinolacept. These patients received pretreatment with anakinra and were included among the 19 previously exposed patients described above.

DITRA

Individual data were obtained from nine patients. All had been treated with anakinra, and one had also received canakinumab. Three of eight (37.5%) were female. One patient had missing data. Two patients were from Morocco, and one patient each was from Tunisia and Denmark. The origins of the remaining patients were not reported. Onset disease was localized in four patients (two for the diaper and scalp, two for the elbow and perineum) and generalized in four patients. During disease evolution, the disease worsened, presenting with

erythroderma or pustules in all patients for whom data were available. The process was accompanied by fever in four of six (66.6%) patients and elevation of acute inflammation reactants in five of six (83.3%) patients. The ages at onset and disease diagnosis varied from neonate to adulthood (14 days to 47 years and 3 months to 54 years, respectively). The delay in diagnosis ranged from 2 months to 17 years. All patients previously received other treatments, including corticosteroids in seven patients, acitretin and ciclosporin in six patients each, methotrexate in four patients, cyclosporine in three patients, and adalimumab and infliximab in two patients each.

Evidence of Different Genotypic Variations in Patients with DIRA/DITRA Treated with IL-1 Inhibitors

DIRA

Nine different mutations in *IL1RN*, showing a homozygous genotype in all cases, were described among patients with DIRA treated with anti-IL-1 drugs in the included studies. A genomic 175-kb deletion on chromosome 2 was observed in patients #6, #7, #11, #13, and #15; two nonsense mutations were detected in patients #2, #3, and #10 (c.229G → T) and patients #4 and #5 (c.160C → T); a 15-bp frame deletion (c. 213_227delAGATGTGGTACCCAT resulting in p.Asp72_Ile76del) was observed in patients #8 and #9; 2-bp (c.156_157delCA) and 22-kb[1] frameshift deletions were identified in patients #1 and #18, respectively; and an intronic variant of unknown clinical significance in the *IL1R1* gene (position c.840, 6 bp upstream of the exon 9 splice-acceptor site), which could potentially interfere with transcript splicing machinery, was found in patient #14. Additionally, the p.R26X *IL1RN* mutation was observed in patient #16, c.396delC nucleotide deletion was observed in patient #17, and both p.Ile74_Pro78del and p.Gln48Thr

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[1] This frameshift spans four exons (two coding) of *IL1RN*, *Q54X*, and an unreported intronic variant of unknown clinical significance in the *IL1R1* gene. This variant resides at position c.840, 6 bp upstream of the exon 9 splice-acceptor site and could potentially interfere with transcript splicing.

IL1RN mutations were observed in patient #19. No mutation analysis was performed in patient #12.

DITRA

Thee different homozygous and heterozygous mutations in *IL36RN* were described among patients with DITRA treated with anti-IL-1 drugs in the included studies. *IL36RN* c.80T > C (p.Leu27Pro) was the most frequent homozygous mutation, present in patients #1, #4, and #8. Patient #8 also presented a microduplication including the *NSD1* gene (5q35.2-q35.3). Homozygous mutation at c.115 + 6T > C in patient #3 was also reported. Patient #6 was diagnosed with an homozygous mutation for *IL36RN*, but the position was not reported. Regarding heterozygous mutations, patients #2, #6, and #8 were identified as carriers of *IL36RN* c338C > T (pSer113Leu) at exon 5, in patients #2, #6, #8, and #9. Patients #8 and #9 also presented a heterozygous mutation in *IL36RN* c.142C > T (p.Arg48Trp) and *NLRP3* c.2107C > A (p.Gln703Lys) at exon 3, respectively.

Evidence for Efficacy and Safety of IL-1-Based Agents in Treatment of DIRA/DITRA

DIRA

We obtained individual data for 17 patients treated with anakinra and 2 patients treated with canakinumab. Length of therapy varied between 2 weeks and 4.5 years for anakinra and was up to 12 months for canakinumab. The initial dosage of anakinra ranged from 1 to 5 mg/kg/day, with 1 mg/kg/day being the dosage most frequently used, in 9 of 13 patients (69.2%) for whom data were available. The dosage was increased in eight patients up to 2.5–3 mg/kg/day or until achieving clinical and analytical response. Two patients required dosage reduction, one due to achieving therapeutic response and the other due to development of generalized urticaria. In two other patients, the initial dosage was maintained. In 11 patients treated with anakinra, concomitant use of corticosteroids was reported; in nine of these cases, the drugs were finally withdrawn,

and in two cases, dosage reduction was performed. All patients achieved immediate (day–hours) clinical responses, and all but one patient also showed an analytical response. The patient who did not show complete response to anakinra was homozygous for a deletion of approximately 175 kb on chromosome 2q, which harbored six genes from a cluster of IL-1-related genes, i.e., *IL1RN* and genes encoding IL-1 family members 9 (*IL1F9*), 6 (*IL1F6*), 8 (*IL1F8*), 5 (*IL1F5*), and 10 (*IL1F10*) [1].

In the short term (< 12 weeks), 15 (88.2%) patients showed good clinical response. In two cases, response was not reported. Ninety percent of patients for whom data were available in the medium/long term (> 24 weeks) (*n* = 10) showed good response. The nonresponder in this group showed a clinical phenotype of chronic recurrent multifocal osteomyelitis and finally responded to azathioprine, corticosteroids, and intravenous immunoglobulins [18].

In the two patients treated with canakinumab, one showed good immediate, short-term, and medium/long-term response, and the other required dosage increase to achieve good response in the short term. No medium/long-term data were available for this patient.

With respect to drug safety, anakinra was associated with some adverse events, including transient injection-site reactions (*n* = 3) and anaphylactic reactions (*n* = 2). An episode of vomiting and diarrhea was reported in a patient treated with high dosage of canakinumab. Finally, subsequent discontinuation of anakinra in nine patients was reported following a flare-up of their disease.

Aggregated data from six patients with DIRA treated with rinolacept were reported in an intervention study with follow-up visits at 3, 12, and 24 months. These patients had previously received anakinra, and their data were among those published individually, corresponding to patients #8, #9, #10, #13, and #15. The sixth patient corresponded to one of those included in the article by Aksentijevich et al. (Table S1 of Supplementary Information). All patients were treated with an initial bolus of 4.4 mg/kg/dose rilonacept and were discharged on 2.2 mg/kg/week. All except one patient required rilonacept dosage escalation to 4.4 mg/kg/week due to

partial clinical response. All patients remained in clinical and analytical remission. Rilonacept was well tolerated, no serious adverse events were reported, and none of the patients met protocol adverse event criteria for rilonacept dosage reduction or permanent discontinuation. The most common events were upper respiratory infection (100%), otitis media (66.7%), and rash (66.7%). Finally, clinical responses to rilonacept were comparable to those observed with anakinra, although there was a clear preference by relatives and patients for staying on weekly versus daily injections [17].

DITRA

Efficacy and safety data were available for nine patients with DITRA. All patients were treated with anakinra at 2–5 mg/kg/day or 100 mg/day, and one patient was also treated with canakinumab 3 mg/kg every 8 weeks. Duration of anakinra treatment ranged from 3 days to 12 months. With regard to efficacy, 77.8% of patients who received anakinra experienced good initial (hours–days) clinical response. Of these, 33.3% maintained the response in the short term (<12 weeks). In the medium/long term (> 24 weeks), 22.2% of patients continued the treatment. One patient, in whom anakinra had previously failed, received treatment with canakinumab, and this treatment did not prove effective at the initial time or in the short- or long-term analyses [16].

With respect to the safety of anakinra, one case of systemic infection was reported, another one of renal and hepatic laboratory abnormalities, rising white blood cell count, and deteriorating clinical status with progressive pustulation and, finally, pain at the injection site without erythema. No adverse events were reported in the patient who had been treated with canakinumab.

In five of eight patients in whom anti-IL-1 drugs failed, the final therapeutic regimens were etanercept and acitretin [19], adalimumab and methotrexate [20], secukinumab [21], ustekinumab [22], and infliximab [23].

DISCUSSION

Summary of Findings

This is the first scoping review to map and summarize use of drugs targeting the IL-1 pathway in patients with DIRA and DITRA. DIRA and DITRA were first identified in 2009 and 2011, respectively, and clinical experience with use of anti-IL-1 drugs is scarce. The best available evidence is based on results from observational studies, most of which were not published in a public repository with an a priori design. Studies of both diseases have been multicenter, multidisciplinary studies, and the findings of these studies have generally been obtained from public sources, with few authors declaring CoIs.

Anakinra is the most commonly used drug for both diseases. The use of canakinumab is anecdotal, and rinolacept has only been used in DIRA. Patients with DIRA tended to be younger at time of onset and start of treatment, and a delay in diagnosis was common for patients with DITRA. No relationships were observed among initial features, evolution, or response to treatment or in the type of genetic mutations present in patients treated with anti-IL-1 drugs. The effectiveness of these treatments differs in both diseases, with greater efficacy observed in patients with DIRA than in patients with DITRA at all time points. Patients with DITRA typically showed good immediate response, but decreased short- and medium/long-term responses. No relevant differences in safety have been found.

Strengths and Limitations

Methodologically, this study was conducted based on an a priori protocol, previously published in a scientific journal and using the latest standards in scoping review methodology. In each of the phases, at least two researchers were involved. Contact with authors of some of the studies allowed us to clarify important points for analyzing the primary data. This report was made according to the recommendations of the PRISMA Extension for Scoping Reviews.

Limitations related to funding and time prevented us from including some articles written in languages other than English. Additionally, it was not possible to contact some of the authors of the articles in order to reduce the percentage of missing data. This was particularly limiting for articles published in the form of abstracts, because we did not exclude these types of publication. This work is a substudy, and although we believe that the global search strategy was complete and that the development of the three-phase search minimized loss of relevant articles, it is possible that we have not included some papers describing studies related to the research topic. The risk of bias in the studies, the quality of the evidence, and statistical analysis techniques were not evaluated. Finally, this is the first scoping review carried out by this research team; therefore, it is possible that there may have been some other unknown limitations.

Research Gaps

The low number of studies, low quality of evidence based on study design, and lack of an a priori design included in a public repository increase the uncertainty regarding the validity of the results. The studies reported in this review were multicenter, multidisciplinary studies, and these characteristics were more evident for DIRA than for DITRA, because DIRA exhibits greater systemic involvement and is fundamentally a disease of the bone system. The included studies were performed in different countries, mostly developed countries, and this observation was more evident for DITRA than DIRA. Surprisingly, no center participated in more than one study in DITRA articles, whereas in articles on DIRA, the NIH, which included various institutions, was involved in 10 of 15 studies. Finally, the absence or public nature of the funding source and the low number of author CoIs were notable. This may be due to the small market for drugs used to treat rare diseases, which can make drugs extremely expensive. Consequently, many pharmaceutical companies may stop manufacturing these drugs or may not initiate research

and development into new therapies [25]. Based on these above findings, primary studies of higher methodological quality and with a greater number of patients are necessary, and secondary scientific investigations should serve as the basis for development of clinical guidelines. Because DIRA and DITRA are rare diseases, making it difficult to include large numbers of patients and find funding, these studies should be multicenter studies, likely with a reference center (similar to that observed for DIRA), and improvement of public and private financial support is needed.

With regard to knowledge on the epidemiology and genetics of DIRA and DITRA, because the reporting of results has not been systematized, preparation of a summary of the results related to use of anti-IL-1 drugs is complex. Accordingly, it would be useful for study summaries to provide case reports for reporting protocols, such as CARE guidelines [26]. Despite this, it was possible to observe the onset of the disease and the earlier administration of treatments in patients with DIRA versus patients with DITRA. Both of these patient groups exhibited delays in diagnosis, probably due to the characteristics of rare diseases and the need for appropriate technology for genetic diagnosis, which may be particularly important in developing countries. In all of the presented cases, the existence and/or the type and position of the mutation found in *IL1RN* or *IL36RN* genes were reported. Thus, of the 43 [27] and 60 [28] homozygous or homozygous and heterozygous mutations that have been described in DIRA and DITRA, respectively, we found nine and four differences in patients who had received treatment with anti-IL-1 drugs. Given the small number of cases published, it is difficult to find associations between the form of presentation or the severity of the disease and the type of mutation in patients treated with anti-IL-1 drugs.

With regard to efficacy, we have not found validated instruments or severity criteria to evaluate the degree of improvement in patients with DIRA or DITRA following treatment. This makes it difficult to quantify the response. To date, treatment efficacy in studies of patients with DIRA has been measured by assessing

clinical and analytical improvement. In patients with DITRA, the reported response is fundamentally clinical. Based on this limited evidence, patients with DIRA showed higher responses at all measured times and did not exhibit disease recurrence; thus, the dosage of corticosteroids can be reduced while receiving treatment with anti-IL-1 drugs. Only one patient with DIRA, who also presented with chronic recurrent multifocal osteomyelitis, showed disease recurrence when being administered anakinra [18]. However, patients with DITRA who responded well immediately showed only weak short- and medium/long-term response. Thus, these patients should be given alternative treatments. In relation to the best available evidence on use of other biological drugs in DITRA that we have been able to find, Boehner et al. recently published a systematic review on generalized pustular psoriasis, including DITRA patients [38]. Those authors found that anti-TNF (7/8) and anti-IL-12/IL-23(p40) (1/1) drugs also seemed to be effective in DITRA patients. In our study, in five of eight patients in whom anti-IL-1 drugs failed, the final therapeutic regimens were etanercept and acitretin, adalimumab and methotrexate, secukinumab, ustekinumab, and infliximab. Only one patient with DITRA who had poor response to etanercept and experienced relapse after adalimumab was treated successfully with anakinra [37].

With respect to safety, data from observational studies are unreliable, and cases of paradoxical generalized pustular psoriasis, and worsening of the disease or severe infections after anti-TNF and anti-interleukin 1 treatments have been described in literature. Thus, our observations suggest that DITRA patients may experience a better response with a similar safety spectrum with anti-TNF, anti-IL-12/IL-23(p40) or anti-IL-17 drugs as compared with other molecules blocking the IL-1 pathway [39, 40]. With regard to concomitant use of corticosteroids, only one case was reported, and worsening of the disease was observed [22].

The response to canakinumab and rinolacept was generally similar to that to anakinra for both diseases in the reported cases. No differences were observed in the safety of these treatments in both diseases. Finally, no relationships between the location of the genetic mutation and the response to treatment were observed; For example, genetic alterations were present in the one patient [1] with DIRA who did not respond completely to anakinra treatment, but were also present in the other four patients (#5, #29, #30, and #31) who did respond to treatment.

CONCLUSIONS

Available evidence on use of anti-IL-1 drugs in patients with DIRA and DITRA is scarce and based on observational studies. Anakinra is the most commonly used drug in patients with DIRA or DITRA, and most experience with canakinumab has been anecdotal. Rinolacept has only been used in patients with DIRA. There was no apparent relationship between mutations found in patients treated with anti-IL-1 drugs and the onset symptoms, disease evolution, or treatment response. The observed efficacy was high in patients with DIRA at all time points and at the initial (immediate) time in patients with DITRA, but was low at short- and medium/long-term periods in these patients. No differences in safety were found.

Confidence in these results is limited by the lack of available evidence and the type of methodology used in the studies. Systematizing the collection and reporting of cases, standardizing scales of severity measurement, and having greater public/private involvement are necessary to produce primary studies that can be used to answer questions regarding the efficacy, safety, and association of mutations with response to treatments using systematic reviews and metaanalysis techniques.

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